



CLINICAL RESEARCH

Cost-effectiveness analysis of aldosterone blockade with eplerenone in patients with heart failure after acute myocardial infarction in the French context: The EPHEsus study

Analyse coût-efficacité dans le contexte français du blocage de l'aldostérone par éplerenone chez les patients insuffisants cardiaques après infarctus du myocarde : l'étude EPHEsus

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KEYWORDS

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Summary

Background. — The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHEsus) randomized clinical trial demonstrated the efficacy of eplerenone, a new aldosterone antagonist diuretic, with standard treatment versus standard treatment alone in the reduction of cardiovascular mortality and cardiovascular-related hospital readmissions for patients with heart failure after an acute myocardial infarction.

Aim. — We assessed the incremental cost per life-year saved of eplerenone in the French context versus standard treatment.

Methods. — A within-trial study was designed. A piecewise regression model yielded death rates and survival gains adjusted for patients' characteristics, based on the extraction of comparable patients from the Saskatchewan Health database. Resource use was collected alongside the clinical trial data. Only direct medical costs were considered. All costs were in 2003 euros. Costs and outcomes were discounted at 5%.

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MOTS CLÉS

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Prévention

Results. — The overall mortality rate was 14.4% in the treatment group versus 16.7% in the placebo group ($p=0.008$). Combined cardiovascular deaths and hospitalization rates were 26.7% in the treatment group versus 30.3% in the placebo group ($p=0.002$). The discounted survival gain was 3.2 weeks. The incremental cost per life-year saved was €15,382 (95% confidence interval 8274–42,723). Seventy-four per cent of the values of the incremental cost-effectiveness ratio fell under a €15,000 per life-year saved threshold.

Conclusion. — The cost of eplerenone leads to an acceptable level of incremental cost per life-year saved when compared with existing treatments in the cardiovascular domain for the prevention of cardiovascular death and morbidity in patients with heart failure after an acute myocardial infarction.

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Résumé

Contexte. — L'essai EPHEsus a démontré l'efficacité d'éplérénone, un nouveau diurétique antagoniste de l'aldostérone, avec un traitement standard, comparé au traitement standard seul, dans la réduction de la mortalité et du taux de réhospitalisation cardiovasculaires chez des patients insuffisants cardiaques après infarctus aigu du myocarde.

Objectifs. — Le coût incrémental d'éplérénone par année de vie gagnée comparativement au traitement standard a été calculé en France.

Méthode. — Une étude intra-essai a été réalisée. Les taux de mortalité et les gains de survie ajustés aux caractéristiques des patients ont été modélisés sur une population de patients comparables du Saskatchewan (Canada). Les données d'utilisation de ressources proviennent de l'essai. Seuls les coûts médicaux ont été valorisés, en euros (2003). Les coûts et les effets ont été actualisés à 5%.

Résultats. — La mortalité globale était de 14,4% dans le groupe traité contre 16,7% dans le groupe placebo ($p=0,008$). Le taux combiné d'hospitalisation et de décès cardiovasculaires était de 26,7% avec contre 30,3% sans ($p=0,002$). Le gain actualisé de survie était de 3,2 semaines, le coût par année de vie gagnée de 15 382 € (IC à 95% : 8274 €–42 723 €). Soixante-quatorze pour cent des valeurs du ratio coût par année de vie gagnée étaient inférieures à 15 000 €.

Conclusion. — Éplérénone entraîne un niveau acceptable de coût incrémental par année de vie gagnée comparé aux traitements existants de prévention de la morbi-mortalité cardiovasculaire chez les patients insuffisants cardiaques post-IM aigu.

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Background

In Europe, the prevalence of heart failure (HF) varies from 0.4 to 2% [1,2]. In France, the prevalence of patients with HF was estimated to be 500,000 in 1998, with an annual incidence of 120,000 [3]. Forty per cent of patients die within 12 months of the diagnosis, and only 25% of men and 38% of women survive for five years. The incidence and prevalence of severe HF, defined as left ventricular ejection fraction (LVEF) less than 30% and a cardiothoracic index greater than 60%, are known through Épidémiologie de l'insuffisance cardiaque avancée en Lorraine (EPICAL), a study performed in Lorraine, an eastern region of France [4]. The incidence was found to be 225 cases per one million inhabitants, which, when extrapolated to the whole of France, yields an estimated 13,500 new cases of severe HF per year. The incidence increased substantially with advancing age, with two-thirds of patients being over 70 years. In 1999, 28,200 deaths were attributable to HF [5]. HF is the cause of 150,000 hospital admissions and 3.4 million visits per year [3].

The presence of acute myocardial infarction (AMI) increases the risk of HF, particularly in the first days after the ischaemic event. According to the Valsartan in Acute

Myocardial Infarction (VALIANT) registry, 20% of all patients with AMI presented signs and symptoms of HF during hospital stay [6]. The Cholesterol and Recurrent Events (CARE) study found that 22% of patients with an AMI had acute HF; incidence of HF for patients with recurrent AMI was 33% [7]. According to Cowie, the rate of HF as a direct consequence of AMI is 19% [2]. USIK is a French study in patients admitted for an AMI [8]. In this study, 45% of patients had clinically established HF. When extrapolating the data to the whole of France, knowing that 100,000 cases of AMI are registered, the number of patients with HF after an AMI can be estimated at between 19,000 and 45,000 per year.

Patients with HF consecutive to an AMI receive secondary prevention treatment, combining angiotensin-converting enzyme (ACE) inhibitors with diuretics and/or beta-blockers [9]. The Randomized Aldactone Evaluation Study (RALES) mortality trial showed that the administration of low-dose spironolactone, a diuretic with an aldosterone-antagonist effect, reduced mortality of post-AMI patients with severe HF [10]. With spironolactone, however, 10% of men suffer from painful gynaecomastia that may justify stopping treatment. Eplerenone is an aldosterone antagonist that reduces the risk of gynaecomastia. Eplerenone Post-Acute

Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a randomized controlled trial comparing the combination of eplerenone plus standard treatment versus standard treatment alone for secondary prevention of severe cardiovascular events and death for patients with AMI and HF [11]. In this trial, overall mortality was reduced by 15% and cardiovascular rehospitalizations and cardiovascular deaths were reduced by 13%.

The aim of the present study was to calculate the relative cost-effectiveness of eplerenone plus standard treatment versus standard treatment alone in the French context.

Methods

Patient population

The EPHESUS trial included 6632 patients with post-AMI HF, with a mean follow-up of 16 months. Patients were randomized to either standard optimal treatment including ACE inhibitors, angiotensin II receptor blockers, diuretics, statins, beta-blockers, or coronary reperfusion plus 25 mg eplerenone (titrated up to 50 mg/day), or a placebo plus standard optimal treatment (control group).

The economic analysis was a within-trial analysis since no data were available on the evolution of the patients' health status beyond the mean 16-month follow-up period or on the efficacy of treatment. In EPHESUS, the primary endpoints were time to all-cause death or cardiovascular death and first hospitalization for any cardiovascular event. The main secondary endpoints were cardiovascular death and all-cause death, and any hospitalization.

Survival

The results from EPHESUS were used to model the expected number of life-years gained with the reduction of overall mortality through the follow-up period. The model used in our study was based on the original cost-effectiveness analysis performed by Weintraub et al. [12] in the USA, with minor modifications that did not alter significantly the projections of life-years saved.

Two alternative methods were used to predict long-term survival of patients. First, a sample of 2543 patients with HF after an AMI was extracted from the Saskatchewan Health database. Piecewise regressions were used to estimate mortality risk functions over time and thus survival. Adjustment of survival to patients' characteristics was obtained using proportional hazard Cox models. Piecewise regressions were used because the observed mortality did not follow a decreasing exponential: mortality was high during an acute period after initial event, then tended to stabilize, and finally to increase again because of aging. Moreover, dispersion in the acute phase was not high, but tended to increase through time. Second, the Framingham equation was used to compute expected survival for patients included in the EPHESUS trial.

Life-years lost for patients who died during the trial were calculated as a difference between age at death and age- and sex-specific life expectancies derived from the two methods of survival estimations. Patients who survived during the trial duration did not yield any difference in life-

years saved between eplerenone and placebo. A stochastic sensitivity analysis was performed on the difference in the number of life-years gained between both groups, using naive bootstrap. A confidence interval (CI) was also estimated for the incremental cost-effectiveness ratio (ICER) and acceptability curves were established.

Costs

Only direct medical costs were considered in the model, adopting for France a partial societal perspective. Events and related healthcare services were collected alongside the clinical trial data. For hospitalizations, patients' records were classified in the initial north-American cost-effectiveness study using USA diagnosis-related groups (DRGs). Mapping to the French DRG classification was performed. When mapping was possible, the French costs per DRGs were obtained through the National Cost per Stay Survey, which provides for an average full cost per stay in the public sector [13,14]. For a minority of DRGs and cases, mapping was not possible. We then used Schulman et al.'s method to estimate a cost for France [15]. First, we computed an overall conversion rate between US and French costs for DRGs for which mapping was possible. The conversion rate was the ratio for all cases of US cost per DRG weighted by the number of cases in the trial, to the French costs per DRG weighted by the number of cases. The conversion rate then was applied to the US costs for the DRGs for which mapping was not possible.

Diagnostic procedures and visits to physicians were valued using charges obtained from the French National Fee Schedule. For procedures that could not be mapped into the French procedure code, the conversion rate methodology was applied. Drugs were costed using the French Public Prices for 2003. The daily treatment cost for eplerenone was €2558. Costs and outcomes were discounted at a 5% rate, following the recommendations of the French Health Economists Association [16]. All costs are in 2003 euros.

Results

Clinical outcomes

The overall mortality over the trial period was 478 (14.4%) patients in the treatment group versus 554 (16.7%) in the placebo group ($p=0.008$). Combined cardiovascular deaths and hospitalizations were 885 (26.7%) in the treatment group versus 993 (30.3%) in the placebo group ($p=0.002$) (Table 1).

Life-years gained

Using the Saskatchewan database, 20 weeks of life are lost with standard treatment plus placebo versus 17 for eplerenone plus standard treatment. Thus, long-term undiscounted survival is three weeks. Using the Framingham database, 32 weeks of life are lost for patients who receive standard treatment only versus 27 weeks for patients treated with eplerenone: the incremental effectiveness is five weeks (Table 2).

Table 1 EPHEsus endpoints and results.

	Eplerenone (<i>n</i> = 3319)	Placebo (<i>n</i> = 3313)	Relative risk (95% CI)	<i>p</i>
<i>Primary endpoints</i>				
Death from any cause, <i>n</i> (%)	478 (14.4%)	554 (16.7%)	0.85 (0.75–0.96)	0.008
Death or hospitalization for cardiovascular events, <i>n</i> (%)	885 (26.7%)	993 (30.3%)	0.87 (0.79–0.95)	0.002
<i>Secondary endpoints</i>				
Death from cardiovascular causes, <i>n</i> (%)	407 (12.3%)	483 (14.6%)	0.83 (0.72–0.94)	0.005

Table 2 Life-years lost life, discounted at 5%: Eplerenone versus placebo.

	Placebo (<i>n</i> = 3313)	Eplerenone (<i>n</i> = 3319)	Gain	95% confidence interval
<i>Discounted life-years lost</i>				
Saskatchewan data	0.3653	0.3032	−0.0620	−0.1015, −0.0224
Framingham data	0.6137	0.5165	−0.0972	−0.1652, −0.0315

Table 3 Resource use during follow-up.

Event, <i>n</i>	Eplerenone + standard treatment	Placebo + standard treatment	<i>p</i>
Hospitalizations – all cause	2815	2984	0.12
Hospitalization for cardiovascular events	876	1004	0.03
Acute myocardial infarction	268	269	0.19
Heart failure	477	618	0.002
Stroke	73	54	0.73
Ventricular arrhythmia	58	63	0.79
Emergency room visits	1004	1116	0.1
Cardiovascular diagnostic procedures	1.64	1.67	0.34

Resource use during follow-up

Table 3 displays the results for hospital-resource use. In the treatment group, there were 169 fewer hospital admissions for all causes, 128 fewer admissions for cardiovascular causes, the same number of cardiovascular diagnostic procedures, and 112 fewer visits to emergency rooms. Thus, a slight reduction in resource use was observable with eplerenone, but the difference was significant only for hospital admissions for HF.

Costs during follow-up period

The total undiscounted direct medical cost of follow-up during the trial period, excluding the cost of eplerenone, was €4698.7 for the treatment group versus €4814.1 for the placebo group. Eplerenone added an extra cost of €1084.9 for the period of treatment. Costs for rehospitalizations and outpatient diagnostic procedures were slightly lower in the treatment group versus the placebo group. The most important differences in costs were observed for hospitalizations for cardiovascular causes and for HF (Table 4).

Table 4 Average cost in euros per patient during follow-up period: eplerenone versus placebo (no discount).

Item, €	Placebo (<i>n</i> = 3313)	Eplerenone (<i>n</i> = 3319)	Δ (Eplerenone–placebo)	<i>p</i> *
Rehospitalization costs	3473 ± 5.856	3337 ± 5503	−135.7	0.17
Medication costs	1082 ± 885	1090.4 ± 864	−8.3	0.29
Outpatient diagnostic procedure costs	239 ± 719	252.9 ± 646	14.0	0.14
Emergency room visit costs	20.5 ± 57.0	18.6 ± 48.7	−1.9	0.075
Eplerenone costs (€2.511/day)	0	1084.9 ± 573.4		
Total follow-up costs (including cost of eplerenone)	4814.1 ± 6287.5	5783.6 ± 5963.4	969.6	0.12

* Bilateral Student's *t* test.

Table 5 Cost-effectiveness analysis using different discount rates for costs and life years: Saskatchewan and Framingham survival models (with cost €2558/day).

	Placebo (€)	Eplerenone (€)	Δ cost	Δ life years	ICER	95% CI	Percentage <€50,000/ life year gained
<i>Saskatchewan</i>							
No discount	4814	5784	970	0.066	14.672	7903, 41.004	97.9
5% discount	4767	5721	954	0.062	15.382	8274, 42.723	97.9
<i>Framingham</i>							
No discount	4814	5784	970	0.108	8954	4639, 27.909	98.7
5% discount	4767	5721	954	0.097	9819	5159, 30.178	98.8

Incremental cost-effectiveness ratio

The baseline estimation was made using a 5% discount rate for costs and outcomes. The extra cost per life-year saved was €15,382 (95% CI 8274–42,723) when using the estimation model derived from the Saskatchewan database. With no discounting, the ICER with the Saskatchewan data dropped to €14,672 per year-of-life saved, and €9819 (95% CI 5159–30,178) using the Framingham data to estimate survival (Table 5).

Stochastic sensitivity analysis

A stochastic sensitivity analysis of the ICER was performed to obtain an acceptability curve using bootstrapping and 5000 iterations. Assuming a willingness to pay of €15,000 per life year, treatment with eplerenone is accepted in 74% of all cases, and in 99% of all cases with a willingness to pay €50,000 (Saskatchewan estimation of survival, costs, and benefits discounted 5%) (Fig. 1).

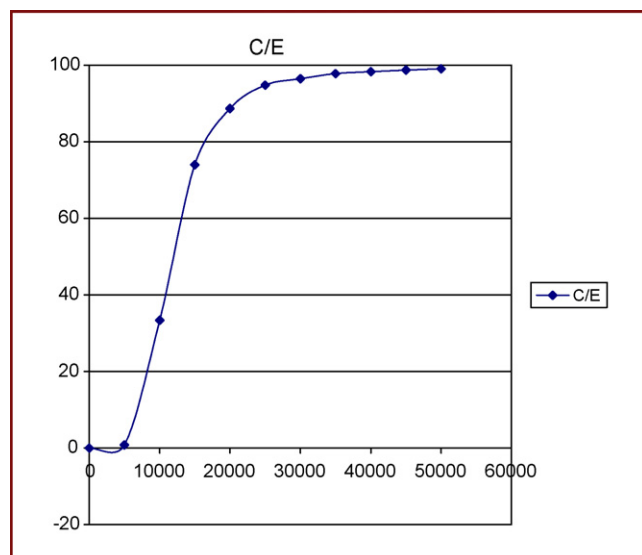


Figure 1. Acceptability curve: Saskatchewan survival data, discount 5%. Cost in €, cost per year of life saved.
Courbe d'acceptabilité: données de survie de la Saskatchewan, actualisation de 5%. Coût en €, coût par année de vie gagnée.

Discussion

The adoption of a within-trial analysis does not allow for full assessment of the cost-effectiveness of the intervention. In real life, patients would probably continue treatment for their lifetime. This choice is always a question of trade-off between the face validity of the extrapolation of outcome and the cost results for the intervention through time and the limits of a censored analysis. In particular, the model may be very sensitive to assumptions made not only on death but also on hospitalization and outpatient procedures, which is why we chose a restrictive model.

In this particular case, outcomes in terms of survival have already been stretched further than the duration of the trial, using either complex modelling from the Saskatchewan database or with the Framingham data. Because the Framingham data were related to patients with HF, and not specifically HF after AMI, the overall gain in survival may have been overestimated. Patients in the Saskatchewan database were similar to those from the EPHEUS trial and the 'piecewise' estimation of the probabilities of death allowed for a better adjustment of survival to the patients' characteristics. Thus, the true cost-effectiveness ratio may be closer to the estimation obtained with the Saskatchewan data.

The overall cost of treatment between the two groups was very similar. There is little potential for cost-saving, although patients treated with eplerenone tend to experience fewer hospital readmissions, and have fewer outpatient diagnostic procedures and emergency room visits, which has some impact on quality of life. Compared to the study by Weintraub et al. [12], we did not use the Worcester Heart Attack Registry because we wanted to keep a conservative approach to estimation of the cost-effectiveness ratio, and the Saskatchewan database delivered the lowest differences in estimates of life-years lost between the two branches. We did not estimate quality-adjusted life years because the data were from only a small subsample of French patients. Moreover, no French value has yet been set for health states described by EQ-5D, the questionnaire used in the trial.

The exclusion of indirect costs, in particular days out of work, should have little impact on the results since the patients' average age in the EPHEUS trial was 64 years and a large proportion would therefore have retired.

Schulman et al.'s [15] conversion method could carry a bias if the admissions or procedures for which there is no

direct mapping between US and French DRGs or procedure codes are very different in terms of relative costs between the two countries. In this study, this bias exists but has a very low impact, since mapping was impossible for less than 2% of all events.

The relatively high variance in the ICER is probably related to the fact that the efficacy of the treatment was short term. The modelling of long-term survival plausibly adds dispersion, since mortality tends to be less predictable with increasing age.

The actual cost per-life year saved (€15,382) can be compared to the cost-effectiveness ratio of other interventions. A cost-utility analysis from the RALES mortality trial has been performed, comparing spironolactone with standard treatment to placebo with standard treatment for the secondary prevention of cardiovascular events and deaths for patients with a severe HF (LVEF < 35%) after an AMI [17]. The follow-up period was 35 months. The study found that results ranged from cost-savings to a maximum cost per quality-adjusted life year of \$US 20,300. The difference with eplerenone can be explained by the low price of spironolactone, which had been on the market for a long time when the trial was performed, by the selection of a high-risk population, and by the duration of follow-up. This suggests that the cost-effectiveness ratio of eplerenone may be improved if targeted towards patients with severe HF. The RALES economic evaluation study did not include a valuation of the main secondary effect of spironolactone, which was painful gynaecomastia, which eplerenone reduces significantly.

Using CODECS, the French documentary database on health-economic evaluation, eight cost-effectiveness studies were selected in the cardiovascular field with results in terms of cost per life-year saved. Full comparison with the results from the present study must be interpreted with caution: it requires some actualization for prices and potential improvements in technology. Moreover, older studies seldom comprise a stochastic sensitivity analysis on the cost-effectiveness ratio and thus do not publish confidence intervals. Published data nevertheless give a relevant order of magnitude. For example, the cost per life-year saved of heart transplantation was €17,626 in 1992 in France [18]. The ICER of recombinant tissue plasminogen activator versus streptokinase for the prevention of thrombotic events in the acute phase of AMI was €12,190 in 1994 [19]. Thus, secondary prevention of cardiovascular events and deaths for post-AMI patients with eplerenone and a standard treatment compares at least with two well-accepted treatments in France.

In the USA, and with a 3% discount rate, the incremental cost per life-year saved was \$US 21,876 (€17,304 using the July 2006 exchange rate) [12]. Croom and Plosker [5] reviewed existing economic studies performed in other countries, and a Swiss study has since been published. All use the same model structure, and their conclusions are quite similar. In Germany, the ICER ranged from €6956 to €14,628 according to the different scenarios [5]. In Spain, the discounted ICER with the Saskatchewan scenario was €11,530 [20]. In the Netherlands, according to Croom and Plosker [5], the ICER ranged from €5635 to €12,795. Finally, in Switzerland, the discounted ICER for the Saskatchewan scenario was CHF 16,178 (€10,392 using the July 2006 exchange rate) [21]. Differences in ICER tell us more about differences in

cost level and structure in the different countries than about differences in cost-effectiveness per se. But in all countries, the ICERs compare favourably to those of other accepted interventions.

Conclusion

Combining the standard treatment of HF after an AMI with an aldosterone-blockade drug, eplerenone, is effective in preventing overall mortality, cardiovascular mortality, and rehospitalizations. The gain in survival over the long term is modest, but the incremental cost of eplerenone leads to an acceptable level of incremental cost per life-year saved when compared to existing treatments in the cardiovascular field.

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